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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
02/28/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/718,163	DEBENEDETTI ET AL.	
	Examiner	Art Unit	
	J. E. Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-13,15-25,27-41 and 43-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-13,15-25,27-41 and 43-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 11/29/07.

The amendment filed 11/29/2007 is acknowledged and has been entered.

1. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claims 1, 3-13, 15-25, 27-41, 43-56 are currently pending and are examined herein.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-13, 15-25, 27-41, 43-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

> Methods comprising administering directly to a cell a mRNA sequence or a DNA sequence encoding said mRNA sequence, wherein the mRNA sequence comprising a translatable sequence encoding a toxin and an untranslatable sequence that inhibits translation of the toxin sequence under conditions that exist within normal mammalian cells that do not overexpress eIF4E but which allows translation of the toxin sequence under conditions that exist within mammalian cells that overexpress eIF4E relative to normal cells and wherein the untranslatable sequence comprises a hairpin secondary structure conformation having a stability measured as folded state free energy of $\Delta G <$ about −50 Kcal/Mol;

does not reasonably provide enablement for the full scope encompassed by the claims; specifically the claims are not enabled for any route of administration other than administration directly to the target cells. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to methods which encompass administering a either a mRNA sequence or a DNA encoding the mRNA, wherein the mRNA sequence comprising a translatable sequence encoding a toxin and an untranslatable sequence that inhibits translation of the toxin sequence under conditions that exist within normal mammalian cells that do not overexpress eIF4E but which allows translation of the toxin sequence under conditions that exist within mammalian cells that overexpress eIF4E relative to normal cells. The specification discloses that the methods are useful for treating cancer in a subject and claims 25-56 are explicitly drawn to treating cancer in a subject. Therefore the claims encompass the use of a nucleic acid sequence for therapeutic purposes (i.e. gene therapy).

The breadth of the claims

With respect to the mode of administration, the claims are very broad. Specifically, since the claims do not particularly indicate any specific type route of administration, the claims encompass any route of administration, including systemic administration of the therapeutic nucleic acid.

The unpredictability of the art and the state of the prior art

At the time of filing, the relevant art considered gene therapy as a whole to be unpredictable as modes of delivery that would provide efficient expression of genes encoding the therapeutic polypeptide sufficient to provide an alleviation of symptoms related to the target disease or condition had not been developed.

Regarding the administration of the therapeutic nucleic acid to a part of the body other than site of the target cells (in this case, the tumor cells), it is well established in the art that delivery is one of the key problems of gene therapy. For instance, regarding gene therapy in general, Anderson (Nature 1998; 392(suppl):25-30) teaches,

> The challenge is to develop gene therapy as an efficient and safe drug delivery system. The goal is more difficult to achieve than many investigators had predicted… The human body has spent many thousands of years learning to protect itself from the onslaught of environmental hazards, including the incorporation of foreign DNA into its genome. (See p. 25, second paragraph). The ultimate goal of gene therapy research is the development of vectors that can be injected, will target specific cells, will result in safe and efficient gene transfer into a high percentage of those cells, will insert themselves into appropriate regions of the genome (or will persist as stable episomes), will be regulated be either by administered agents or by the body's own physiological signals, will be cost effective and will cure disease. (See p. 30, first paragraph).

Crystal (Science 1995; 270:404-410) also indicates some of the problems regarding gene therapy in general. Specifically, regarding the obstacles of human gene transfer, Crystal teaches, "The [gene transfer] vector (should) be specific for its target, not recognized by the immune system…" (See p. 409, column 2 under "The perfect vector").

Finally, regarding the delivery of gene therapy vectors to tumors, Greco (Frontiers in Biosci. 2002; 7:d1516-1524) teaches,

> The administration of gene therapy vectors requires that they be not only targeted, but also protected from degradation, sequestration or immune attack, in order to reach the appropriate sites for transfection. Although some success has been reported for naked DNA, efficient delivery has been restricted to intratumoral injection. (see p. 1517, paragraph bridging columns 1-2).

Indicating that direct delivery of the nucleic acid to the desired site of transfection is critical for delivering the nucleic acid to the appropriate cells.

The claims encompass a type of gene therapy known as gene directed enzyme prodrug therapy (GDEPT). GDEPT is well known in the art. In general, GDEPT is a two-stage process involving step 1: the administration of a vector encoding a foreign enzyme (e.g. TK) that is selectively expressed in tumor cells, followed by step 2: delivery of a prodrug (e.g. GCV) which is convert into an active (i.e. toxic) form by the enzyme of step 1.

Methods using a GDEPT system utilizing TK/GCV for the treatment of solid tumors were well known in the art at the time of filing (see Kirn et al. Trends in Mol. Ned. Vol. 8, Suppl: p. S68-S73; 2002). The known systems utilize tumor-specific promoters to confer tumor-specific expression of TK, which selectively express TK in the tumor cells. The instant invention utilizes a similar system; however, rather than using a tumor-specific promoter to regulate the expression of TK, the applicants have used an element that regulates the expression

of a toxin (such as TK) at the translational level. Specifically, the instant invention involves using an mRNA comprising a UTR that confers tumor-specific translation/expression of a toxin. The UTR allows the translation of the toxin in the presence of eIF4E (a polypeptide involved in initiating translation) and inhibits translation in the absence of eIF4E. EIF4E is present at low concentrations in wild-type cells and elevated in tumor cells.

Regarding the efficacy of GDEPT therapy, Kirn et al. teaches,

> "Several advantages [of GDEPT] can be defined: enhanced selectivity of toward cancer cells, amplification effects, and bystander cell death. However, technical hurdles related to the delivery of the foreign gene by viral or non-viral vectors remain to be overcome before reaching therapeutic success. Thus the main requirement for the future is efficient targeting and delivery." (Emphasis added; see p. S72 under Concluding Remarks).

Thus, Kirn et al. teaches that targeting and delivery of the therapeutic gene is a critical obstacle that must be addressed, which is consistent with the teachings of Anderson, Crystal and Greco, as indicated above.

Working Examples and Guidance in the Specification

The specification discloses working examples that a DNA sequence (i.e. UTK) can be administered to mouse mammary cells in vitro (both wild-type and tumorigenic cells) resulting in an increased cytotoxic effect on tumorigenic cells compared to the controls when GCV is administered (see Table 2, p. 12). Similar effects are seen in human breast cells in vitro (see Example 4, p. 12). The specification also discloses by example that the DNA sequence (i.e. UTK) can be administered to tumor cells in immunologically impaired mice (in vivo) by direct administration and by systemic administration, resulting in a tumor-specific toxic effect compared to the controls (see Examples 5 and 6, p.14-18).

However, the working examples compare effectiveness of the claimed DNA sequence (i.e. UTK) to a control DNA sequence that constitutively expresses the toxin (TK) in all cell types. It was known in the art that tumor-specific expression of the toxin was critical for effective therapeutic treatment (see above). The GDEPT systems known in the art utilized tumor-specific promoters to confer tumor-specific expression of TK. However, this type of system is still plagued by unpredictable and unreliable results (see above). In order to overcome the unpredictability of tumor treatment using a GDEPT system recognized in the art, the specification would have to show examples that the instant invention overcomes the recognized obstacles and shortcomings. To do this the working examples would have to show that regulating the expression of the toxin (TK) at the translational level overcomes the art recognized problems regarding systemic administration of the nucleic acid in subjects that have a fully functional immune response. However, the working examples only show systemic administration of a DNA to an immunocompromised mouse. There are no working examples show systemic administration of a DNA to a mouse that has a fully functional immune system. Therefore, there are no working examples showing that the claimed invention overcomes the unpredictability recognized in the art.

Quantity of Experimentation

The art recognizes that a high level of experimentation is required for the development of a viable and efficacious GDEPT cancer therapy. For example, Kirn et al. (Trends in Mol. Ned. Vol. 8, Suppl: p. S68-S73; 2002) teaches that the progression of suicide gene therapy approaches to the clinic will require further investigations into effective tumor targeting and vector delivery

(see p. S70, second paragraph). Furthermore, Anderson, Crystal and Greco all provide evidence that systemic delivery of a therapeutic nucleic acid sequence is unpredictable because of, among other things, the host's immune response.

The quantity of experimentation to determine the reliability and efficacy of the proposed GDEPT system is very large.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability recognized in the art, the breadth of the claims, the lack of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed method to its full scope is undue.

Response to Arguments

3. Applicant's arguments filed 11/1/2007 have been fully considered.

4. The Declaration under 37 CFR 1.132 filed 11/1/2007 is sufficient to overcome the rejection of claims rejected under 35 U.S.C. 102(a).

With respect to the scope of enablement rejection, it is noted that the only issue still remaining is the mode of administration. With respect to the rejection as it stands, Applicants argue that the specification provides in vitro and in vivo working examples that provide enablement for the full scope of the instant claims. Applicants assert that in the present

invention, the genes may target any cell within the subject but will show a therapeutic effect only in tumor cells due to specificity of the presence of eIF4E.

In response, it is acknowledged that the therapeutic effect of the present invention would only be seen in tumor cells. However, what applicants fail to appreciate is that the nucleic acid must first find the tumor cells. When administering the claimed nucleic acid into a subject, there is no particular mechanism to ensure that the nucleic acid will reach its target destination (tumor cells). First the target tumor cells represent only a miniscule fraction of millions of cells in a subject. Second, even if the nucleic acid could potentially randomly reach the target cells in a subject, the art recognizes that the nucleic would be prone to attack from the host's immune system (e.g., see Crystal and Greco above). It is also noted the Kirn teaches that the progression of suicide gene therapy approaches to the clinic will require further investigations into effective tumor targeting and vector delivery. Therefore, it is unpredictable, without evidence to the contrary, that the claimed nucleic acid could be systemically administered to a subject that has a functional immune system and be able to effectively reach it's the target tumor cells. Applicant's in vivo data is insufficient to overcome these art-problems because the in vivo experiments were performed on mice that had a compromised immune system. Therefore, it is still unpredictable that the results found in the working examples for systemic administration could be successfully completed in vivo in a subject having a functional immune system. It is noted that the evidence of record does provide an enabling disclosure for delivering the nucleic acid directly to the tumor cells. That is, the animal model used is recognized as an appropriate model for direct delivery, but not for systemic delivery because the animal model used doe not have a fully functional immune system.

With respect to the literature references which Applicants refer to, Applicant is respectfully reminded that MPEP § 2164.01 indicates that the application, when filed, must contain sufficient information to enable one of skill in the art how to make and use the claimed invention. In other words, the claims must be enabled at the time of filing. In the instant case, in view of the art of record which demonstrates that delivering a nucleic acid to specific target cells by general, non direct-delivery is unpredictable, and in view of the originally filed specification which only provides guidance for direct delivery, the specification at the time of filing does not provide an disclosure which enables the full scope encompassed by the claims.

Furthermore, in view of the teaching of the indicated prior art, the amount of further experimentation that is required to overcome the art-recognized problems is beyond routine and would constitute a significant and unexpected advancement over the state of the art at the time of filing. In other words, the amount of additional experimentation required to enable the instant claims to their full scope is undue.

Therefore, Applicants arguments are not persuasive.

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. E. Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 8:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. Angell/
Primary Examiner, Art Unit 1635